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(12) # EUROPEAN PATENT APPLICATION

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(54) **Long acting injectable formulations containing hydrogenated castor oil.**

(57) There is disclosed an injectable formulation containing hydrogenated castor oil and an avermectin compound which has been discovered to provide an unexpectedly long duration of activity. The formulation contains the avermectin active ingredient and a suitable amount of hydrogenated castor oil in a physiologically acceptable hydrophobic non-aqueous vehicle. Efficacious levels of the avermectin compounds have been maintained for up to 42 days. Prior injectable formulations provided only 14 days duration of activity, or had other undesirable side effects such as pain and tissue irritation at the injection site.

EP 0 535 734 A1

BACKGROUND OF THE INVENTION

The avermectin series of compounds are potent anthelmintic and antiparasitic agents against internal and external parasites. The natural product avermectins are disclosed in US 4,310,519 to Albers-Schonberg et al., and the 22,23-dihydro avermectin compounds are disclosed in Chabala et al. US 4,199,569.

SUMMARY OF THE INVENTION

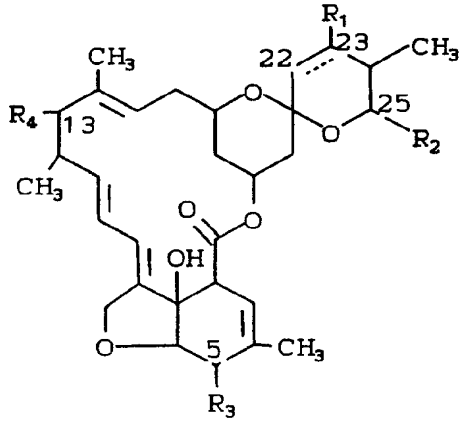
This invention is concerned with the unexpectedly long duration of activity which is observed when avermectin injectable formulations are prepared using hydrogenated castor oil and hydrophobic or water immiscible carriers. Thus, it is an object of this invention to describe such a prolonged therapeutic effect. An additional object is to describe the avermectin compounds which may be employed in the long acting formulation. A still further object is to describe additional components which may be employed in the formulation. Additional objects will become apparent for a reading of the following description.

DESCRIPTION OF THE INVENTION

This invention consists of an injectable formulation of a hydrogenated castor oil and an avermectin compound in a hydrophobic carrier which has been found to have a considerably prolonged duration of activity against internal and external parasites.

The hydrogenated castor oil imparts to the formulation an increased viscosity. While not wishing to be bound by theory, it appears that the increased viscosity together with the hydrophobicity of the carrier enable the injected formulation to remain at the injection site and form a "depot" of the active material which is slowly removed from the injection site over a prolonged period of time. The hydrogenated castor oil is readily prepared using normal techniques known to those skilled in the art of preparing hydrogenated castor oils and one suitable form of hydrogenated castor oil is available commercially under the trade name "Thixcin" from NL Industries.

The avermectin compounds have the following structure:



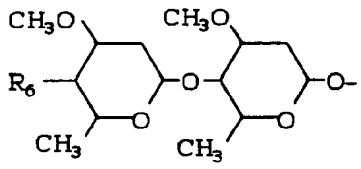
where the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 8 carbon atoms;

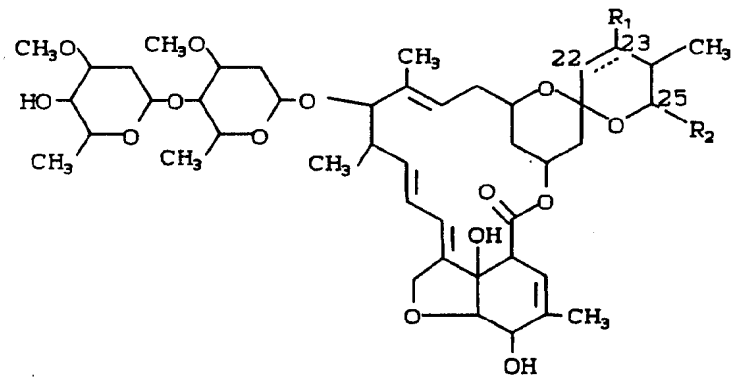
R_3 is hydroxy, methoxy or = NOR_5 where R_5 is hydrogen or lower alkyl; and

R_4 is hydrogen, hydroxy or



where R_6 is hydroxy, amino, mono-or di-loweralkyl amino or loweralkanoylamino.

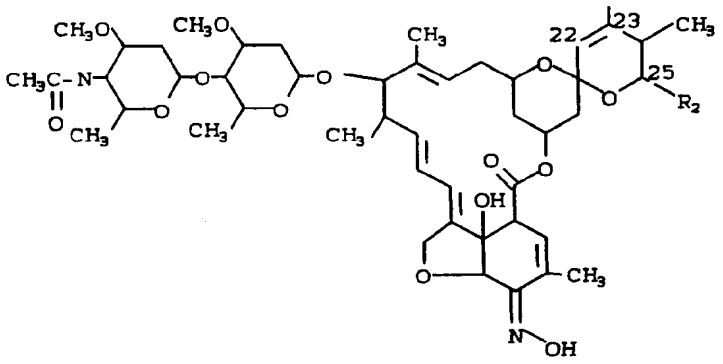
The preferred compounds are avermectin Bla/Blb (abamectin), 22,23,dihydro avermectin Bla/Blb (ivermectin) and the 4"-acetylamino-5-ketoximino derivative of avermectin Bla/Blb. Both abamectin and ivermectin are approved as broad spectrum antiparasitic agents. The structures of abamectin and ivermectin are as follows:



wherein for abamectin the broken line represents a double bond and R_1 is not present and for ivermectin the double bond represents a single bond and R_1 is hydrogen; and

R_2 is isopropyl or sec-butyl.

The 4"-acetyl amino-5-ketoximo derivatives of avermectin Bla/Blb has the following structural formula:



where R_2 is isopropyl or sec-butyl.

The avermectin products are generally prepared as a mixture of at least 80% of the compound where R_2 is sec-butyl and no more than 20% of the compound where R_2 is isopropyl.

The instant formulation is equally applicable to other compounds used for injection as long as such compounds are soluble in the mixture of the hydrogenated castor oil and hydrophobic carrier. Compounds that can be used in this formulation are, antiparasitic agents, antibiotics, therapeutic vitamin and mineral supplements, growth promoting agents, hormones, and other agents that are assisted in their therapeutic effect by having their effects extended over a prolonged period of time.

In the injectable forms of the avermectin formulation it has not been possible to provide a long acting formulation since the avermectins are insoluble in water and generally of low solubility in the oil carriers usually used for injection. Heretofore, injectable formulations of a maximum of 14 days have been possible. The current long acting formulations of avermectins provided for unacceptably large volumes of the injection fluid, or resulted in irritation at the injection site.

The instant formulations of an avermectin compound with hydrogenated castor oil in a hydrophobic carrier provides the advantages of a readily injectable formulation which provides the animal with treatment and protection against internal and external parasites for up to 42 days. The hydrogenated castor oil increases the viscosity of the formulation when present at from about 0.5 to 3% on a weight for volume basis. The material forms a depot and remains generally in the area of the injection site, however, it is still readily drawn into a syringe and expelled from the syringe into the tissue of the injection site, usually subcutaneously, without undue force being applied to the syringe. The increased viscosity and hydrophobicity of the injection material causes the material to be maintained as a depot to provide the necessary reservoir of active ingredient for a long acting effect. No pain or tissue damage has been observed at the site of injection either at the time of injection or during the 42 day course of therapy. In contrast to most oil based formulations, the formulation maintains a low viscosity even at high drug loads and even at temperatures as low as 5 ° C, a temperature at which most oil-based formulations become too viscous for practical use. Since previous injectable formulations only provided 14 days duration, the improved current formulation with 42 days duration avoids two additional injections which would be necessary to obtain 42 days protection with a 14 day duration injection and also avoids the stress of the extra handling necessary for the extra injections which increses illness and weight loss.

The hydrogenated castor oil formulation contains the avermectin compound in a hydrophobic physiologically acceptable injection solvent in which the avermectin compound is readily soluble. Any physiologically and pharmaceutically acceptable carrier may be used so long as the avermectin compound is soluble therein. Examples of such carriers are glyceryl triacetate (Triacetin), distilled acetylated monoglycerides (Myvacet), miglyol 812, safflower seed oil and the like, or a combination of such carriers. The formulations will generally be prepared to administer from 0.1 to 1 mg/kg preferably from 0.4 to 0.85 mg/kg and most preferably from about 0.6 to 0.7 mg/kg of the active ingredient. At a preferred dose volume of about 1 ml to treat 50 kg of animal body wight the formulation contains from 5 to 50 mg of avermectin compound per ml of solution or about 0.5 to 10% w/v preferably 2.5 to 5% w/v. However, depending upon the activity of the compound and the animal being treated, doses as low as 0.3% w/v of the avermectin compound are usable.

In addition to the hydrogenated castor oil, the avermectin and the hydrophobic carrier, the formulation can contain an antioxidant such as a propyl gallate, BHA (butylated hydroxy anisole), BHT, (butylated hydroxy toluene) monothioglycerol and the like. The antioxidants are generally added to the formulation at rates of from 0.01 to 2.0% (w/v).

Since the long acting formulation is intended for injection, it is necessary that it be sterilized. Heat sterilization is generally to be avoided since the avermectin compound would be unstable at autoclave temperatures. Rather, membrane sterilization is preferred. The sterile solution is then packaged aseptically.

The avermectin-hydrogenated castor oil long acting injectable formulation may be administered to warm blooded animals to provide up to 42 days of treatment and protection against external and internal parasites. Typically, the formulation is administered to domesticated animals such as cattle, sheep, pigs, dogs, horses, and the like.

The following example is provided in order that the invention might be more fully understood. It is not to be construed as a limitation of the invention.

EXAMPLE OF THE INVENTION

An ivermectin formulation for injection was prepared from the following formula:

Ivermectin	3.15% w/v
n-Propyl gallate	0.02% w/v
Hydrogenated Castor Oil (Thixcin)	1.5% w/v
Glyceryl triacetate (Triacetin)	qs 100% w/v

Into a tared beaker 12.6 gm of ivermectin and 0.08 gm of n-propyl gallate are dissolved in 300 ml of glyceryl triacetate. The materials are filtration sterilized and placed in a dispersator/mixer, heated to about 50 ° C and the dispersator/mixer stirred at about 400 rpm. 6.0 gm of hydrogenated castor oil previously

sterilized by gamma radiation is added into the warm solution with mixing. To the beaker is then added sufficient filtration sterilized glyceryl triacetate to prepare a 400 ml solution. A thickening of the solution is observed. The stirring rate is then increased to about 4000 rpm and the stirring is continued at 4000 rpm for about 25 ± 5 minutes. The stirring rate is reduced to about 400 rpm and the solution allowed to cool to ambient temperature. The solution is then packaged aseptically and stored at room temperature. No separation of the solution was observed. The viscosity of the solution was 500 +/- 100 cps as measured by a Brookfield viscometer with a spindle #2 at 25 ° C and 60 rpm.

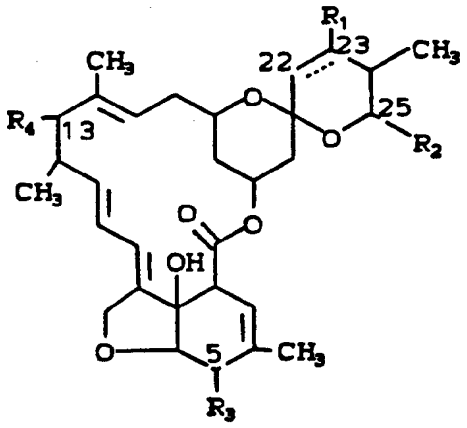
The sterile viscous ivermectin solution was injected into calves at a dose of 630 mcg/kg at a dose volume of between 5 and 10 ml depending upon the weight of the animal. Randomly selected groups of animals were challenged with infection levels of Cooperia spp and Nematodirus helvetianus on days 28 and 42. The single injection of ivermectin was seen to be fully effective against the challenges to day 42.

Claims

1. An injectable composition consisting of from 0.5 to 10% w/v of an avermectin compound in a pharmaceutically acceptable hydrophobic carrier and from 0.5 to 3% w/v of a hydrogenated castor oil.

2. The long acting injectable formulation of Claim 1 where the hydrogenated castor oil is present at from 0.5 to 3% w/v of the formulation.

3. The composition of Claim 1 wherein the avermectin compound has the formula:



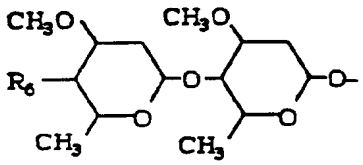
wherein the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 8 carbon atoms;

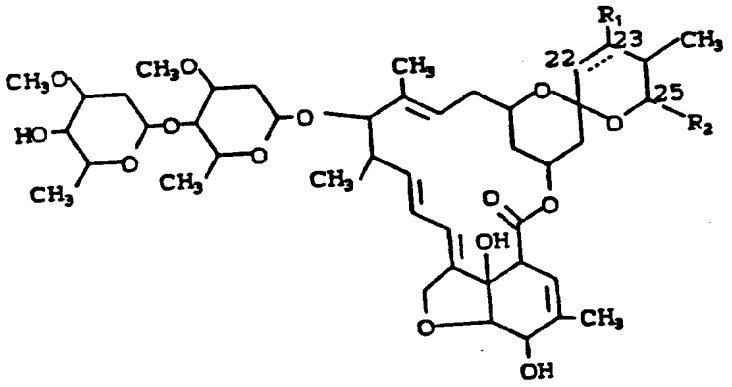
R_3 is hydroxy, methoxy or = NOR_5 where R_5 is hydrogen or loweralkyl; and

R_4 is hydrogen, hydroxy or



where R_6 is hydroxy, amino, mono- or di-loweralkyl amino or loweralkanoylamino.

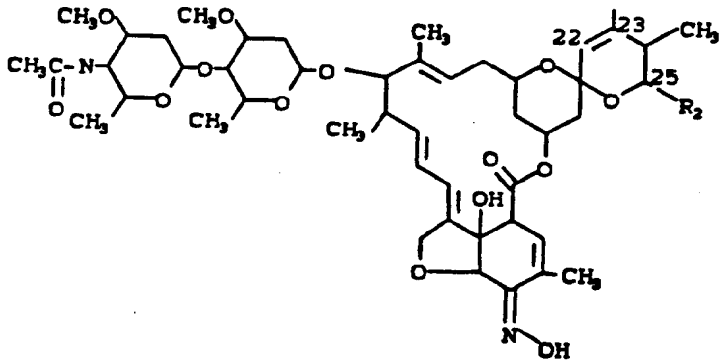
4. The composition of Claim 2 wherein the avermectin compound has the formula:



wherein for abamectin the broken line represents double bond and R_1 is not present and for ivermectin the double bond represents a single bond and R_1 is hydrogen; and

R_2 is isopropyl or sec-butyl.

5. The composition of Claim 3 wherein the avermectin compound has the formula:



where R_2 is sec-butyl or isopropyl.

6. The composition of Claim 4 where the avermectin compound is ivermectin.

7. The formulation of Claim 1 which contains from about 5 to 50 mg of the avermectin compound per ml of formulation.

8. The process of Claim 1 where the hydrophobic carrier is glyceryl triacetate, distilled acetylated monoglycerides, miglyol 812, safflower seed oil or mixtures thereof.

9. A process for the preparation of the composition of Claim 1 which comprises dissolving the avermectin compound in the pharmaceutically acceptable hydrophobic carrier; dissolving the optional antioxidant in the resulting solution; heating the solution to about 50 ° C; adding the hydrogenated castor oil; mixing the resultant solution in a high speed mixer at about 4000 rpm for about 25 minutes.

10. The use of a composition of Claim 1 for the manufacture of a medicament for the treatment of internal and external parasites of animals.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 2940

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X Y	GB-A-2 176 182 (GLAXO GROUP LIMITED) * page 1, line 35 - line 61 * * page 4, line 30 - line 45 *	1-3,7-10 4-6	A61K31/71 A61K47/44 A61K9/00
Y	EP-A-0 413 538 (MERCK & CO. INC.) * claims 1-10 *	4-6	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17 NOVEMBER 1992	VENTURA AMAT A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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